

Title    Reactive Oxygen Species Implicated in the Toxicity  
            and Cytotoxic Action of Certain Anticancer Agents.

Reactive oxygen species including superoxide anion, hydrogen peroxide and hydroxyl radicals are generated in the mode of action of certain clinically useful anticancer agents. In the anthracyclines this causes lipid peroxidation which correlates with the clinically limiting cardiotoxicity. In bleomycin, tallysomyacin and novel haemiacridines this leads to macromolecular lesions and correlates with cytotoxic and anticancer properties.

GENERATION AND EFFECTS OF OXYGEN RADICALS IN INTACT CELLS, S. Orrenius, Department of Forensic Medicine, Karolinska Institutet, S-104 01 Stockholm, Sweden.

Recent evidence suggests that the cytochrome P-450-linked monooxygenase system can contribute significantly to the generation of oxygen radicals in the intact cell. This can be observed with isolated hepatocytes, where substrate-stimulated autoxidation of cytochrome P-450 and one-electron reduction of quinonic substrates to semiquinone radicals, which can enter redox cycles with  $O_2$ , have been shown to lead to formation of  $O_2^{\cdot-}$ , which is subsequently metabolized to  $H_2O_2$  by superoxide dismutases. Catabolism of  $H_2O_2$  formed in the cytosolic or mitochondrial compartments occurs primarily by the glutathione peroxidase system and is associated with enhanced rates of GSH and NADPH oxidation, which may eventually lead to GSH depletion. Associated herewith there is a perturbation of intracellular calcium homeostasis involving a release of  $Ca^{2+}$  sequestered in both the mitochondria and endoplasmic reticulum. Whereas the mitochondrial  $Ca^{2+}$  release appears to be linked directly to NADPH oxidation as result of mitochondrial hydroperoxide metabolism, the impairment of  $Ca^{2+}$  sequestration by the ER seems to be caused by inhibition of the microsomal  $Ca^{2+}$  pump and/or an increased permeability of the membrane to  $Ca^{2+}$  occurring during generation of oxygen radicals in the GSH-depleted state. The available evidence suggests that the perturbation of normal calcium homeostasis may be an early and important event in the development of cytotoxicity during oxidative stress.